REMARKS

Claims 1-37 were previously canceled without prejudice to the Applicants' rights to pursue the subject matters in a future application. Claims 38-117 were previously added and are currently pending in this application. By this Amendment, Applicants canceled claims 118-121, amended claims 77, 89-93 and 110-116, and added new claims 122-125. Support for new claims 122-125 can be found *inter alia* on page 17, lines 27-35, and page 18, lines 1-16 of the Specification.

Support for "mixing the anti-resorptive agent into the polymer component before the polymer component is mixed with the liquid monomer component" is found *inter alia* on page 16, lines 27-29 of the Specification.

Support for mixing the dry polymer component with the liquid monomer component to obtain polymerize bone-cement matrix can be found *inter alia* on page 13, lines 12-19 of the Specification.

Support for "when impregnating the bone-cement dough with the anti-resorptive agent…, the anti-resorptive agent's particle size is about the same or less than the size of the bone-cement's particles" can be found *inter alia* on page 17, lines 20-23 of the Specification.

For impregnating the anti-resorptive agent in the bone-cement dough, the particle size of the anti-resorptive agent is dependent on the particle size or profile of the dry polymer component. *See*, for example, page 15, lines 10-17, page 17, lines 20-27 of the specification.

The appropriate particle size of the anti-resorptive agent is readily achieved by grinding and sifting through the

appropriately sized mesh screens. *See* page 17, lines 24-26 of the Specification.

Support for "anti-resorptive amount" can be found *inter alia* on page 17, lines 27-35, and page 18, lines 1-16 of the Specification.

Support for impregnating or loading bone-cement with anti-resorptive agents without affecting the biomechanical properties of the polymerized bone-cement, the chemical structure of the anti-resorptive particles, and/or the polymerization of the bone-cement components can be found *inter alia* on page 18, lines 32-36, page 19, lines 1-12, and page 38, example 1 of the Specification.

Support for "local delivery of bisphosphonates to the bone surrounding prosthetic implant" can be found *inter alia* on page 32, lines 8-27, and page 40, example 3 of the Specification.

Support for "arresting the process of aseptic loosening attributed to osteoclasts" can be found *inter alia* on page 1, lines 25-28, page 4, lines 25-26, page 8, lines 6-9, page 17, lines 27-33 of the Specification.

Accordingly, there is no issue of new matter and Applicants respectfully request the entry of this Amendment. Upon entry, claims 38-121 are pending and under examination.

I. Response to Argument

1. Anuta and Lehtinen do not teach or motivate one skilled in the art how to make or use Applicants' claimed invention

The Examiner states that "the rejection made in the paper mailed 24 June 2004 under 35 U.S.C. section 103(a) over Anuta [U.S. Pat. No. 4,341,691] and Lehtinen [U.S. Pat. No. 5,733,564] is maintained and hereby repeated..." *See* page 2, second paragraph of the January 13, 2005 Office Action.

The Examiner further states:

> It would have been made obvious to one of ordinary skill in the art at the time it was made to employ the recited particle sizes motivated by the recitation of Anuta that Zimmer's standard bone cement employs a mixture of 65-70% polymer beads with a maximum average size of 25 microns and 30-35% of the beads have been milled (column 5, lines 43-47) and a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns (column 6, lines 59-63). *See* page 3, paragraph 1 of January 13, 2005 Office Action. *See also* page 4, lines 15-21 of June 24, 2004 Office Action.

The Examiner concedes that Anuta "does not teach the addition of bisphosphonates." *See* page 3, paragraph 1 of the January 13, 2005 Office Action. *See also* page 4, lines 21-22 of June 24, 2004 Office Action.

The Examiner further states:

> It would have been obvious to employ a bisphosphonate in the bone cement motivated by the teaching of Lehtinen who teaches that bisphosphonate's main effect is their ability to inhibit bone resorption (column 3, lines 21-23). Such a modification would have been motivated by the reasoned expectation of producing a bone-cement, which is effective in comprehensively inhibiting bone resorption. *See* page 3, paragraph 1 of the January 13, 2005. *See also* page 4, last sentence and page 5, lines 1-4 of the June 24, 2004 Office Action.

In response, Applicants respectfully traverse the Examiner's above ground(s) of rejection.

1.1 Anuta

Column 5, lines 43-47 of Anuta, as cited by the Examiner, states:

> The poly methyl methacrylate powder in Zimmer's standard bone cement is comprised of 65 to 70% polymer beads with a maximum average size of 25 microns, (regular beads), and 30 to 35% of the polymer beads which have been milled.

Column 6, lines 59-63 of Anuta, as cited by the Examiner, states:

> Alternatively, a bead fraction, where the bead powder is sifted to a size range of less than 13 to 17 microns can be substituted for the milled bead fraction, and will impart characteristics similar to the above-described milled bead fraction.

1.2 Lehtinen

Column 3, lines 21-23 of Lehtinen, as cited by the Examiner, states:

> The main effect of the bisphosphonate is their ability to inhibit bone resorption, but contrary to the effect on mineralization, the mechanism involved is cellular.

1.3 Applicants' claimed invention

Applicants' independent claims 38 and 77 recite:

38. A composition for local drug delivery comprising:

(a) a polymeric bone-cement component in the form of particles, and

(b) an anti-resorptive agent in the form of particles,

wherein the anti-resorptive agent's particle-size distribution is about the same or less than the polymeric bone-cement component's particle-size distribution.

77. A composition for local drug delivery comprising:

(a) a monomeric bone-cement component;

(b) a polymeric bone-cement component in the form of particles, and

(c) an amount of an anti-resorptive agent in the form of particles,

wherein the anti-resorptive agent is uniformly mixed with the polymeric bone-cement component first before the polymeric bone-cement component is mixed with the monomeric bone-cement component,

wherein the polymeric bone-cement component comprising the anti-resorptive agent is uniformly mixed with the monomeric bone-cement component to effect a polymerization reaction to obtain a polymerized bone-cement matrix,

wherein the anti-resorptive agent's particle-size distribution is about the same or less than the polymeric bone-cement component's particle-size distribution to provide for even distribution of the anti-resorptive particles throughout the polymerized bone-cement matrix after polymerization reaction, and to prevent the anti-resorptive agent from leaching out at different rates and ensure uniform drug delivery to tissue adjacent to the polymerized bone-cement matrix,

wherein the amount of anti-resorptive agents added to the polymeric bone-cement component does not weaken the bone-cement component or polymerized bone-cement matrix, or interfere with polymerization reaction of the bone-cement components,

wherein the polymerization of the bone cement components does not chemically interfere with or inactivate the anti-resorptive agents, and

wherein the anti-resorptive amount of anti-resorptive agents is the amount of anti-resorptive agent, which is evenly distributed throughout the polymerized bone-cement matrix, sufficient to prevent the loosening of the polymerized bone-cement matrix from a living bone to which is it attached for an extended period of time.

The table below is a comparison of Anuta and Lehtinen and Applicants' claim 38. *See* also a flow chart summary of the bone-cement of Applicants' claimed invention on **Exhibit A**.

Anuta	Lehtinen	Claim 38
		38. A composition for local drug delivery comprising:
The poly methyl methacrylate powder [polymer component - See page 13, line 36 to page 14, lines 1-2 of Applicants' Specification] in Zimmer's standard bone cement is comprised of 65 to 70% polymer beads with a maximum average size of 25 microns, (regular beads), and 30 to 35% of the polymer beads which have been milled. [*See* column 5, lines 43-47 of Anuta] Alternatively, a bead fraction, where the bead powder is sifted to a size range of less than 13 to 17 microns can be substituted for the milled bead fraction, and will impart characteristics similar to the above-described milled bead fraction. [*See* column 6, lines 59-63 of Anuta]	**No Teaching**	(a) a polymeric bone-cement component in the form of particles, and
No Teaching	The main effect of the bisphosphonate is their ability to inhibit bone resorption, but contrary to the effect on mineralization, the mechanism involved is cellular. [*See* column 3, lines 21-23 of Lehtinen] **No Teaching**	(b) an anti-resorptive agent **in the form of particles,** [*See*, for example, page

		17, lines 20-23]
No Teaching	**No Teaching**	**wherein the anti-resorptive agent's particle-size distribution is about the same or less than the polymeric bone-cement component's particle-size distribution.** [*See*, for example, page 17, lines 20-23]

1.4 Anuta and Lehtinen, alone or in combination, do not render the particle size of the anti-resorptive particles obvious

Anuta discloses the particle size distribution of the polymer or particulate component of Zimmer's standard bone cement, which is "comprised of 65 to 70% polymer beads with a maximum average size of 25 microns…, and 30 to 35% of the polymer beads which have been milled…", or "[a]lternatively, a bead fraction, where the bead powder is sifted to a size range of less than 13 to 17 microns can be substituted for the milled bead fraction…" *See* column 5, lines 43-47 and column 6, lines 59-63 of Anuta.

Lehtinen discloses "effect of the bisphosphonate is their ability to inhibit bone resorption…"*See* column 3, lines 21-23 of Lehtinen.

However, **Anuta and Lehtinen**, alone or in combination, do not render Applicants' claimed invention obvious for the following reasons:

(a) A typical bone-cement comprises a dry polymer component and a liquid monomer component (*See* column 1, lines 28-29 of Anuta), and Anuta and Lehtinen does not teach one of ordinary skill in the art which component(s) the anti-resorptive agents

should be added, or whether the anti-resorptive agents should be in the form of particles or a solution.

(b) Lehtinen teaches using a "solution of a bisphosphonate" to treat endo-osteal material. *See* abstract of Lehtinen. The disclosure of Lehtinen would have taught one of ordinary skill in the art away from Applicants' claimed invention, which specifically recites the use of "anti-resorptive agents in the form of particles." *See* claims 38 and 77, and page 17, lines 24-26 of the specification.

(c) Adding anti-resorptive particles to the liquid monomer component will result in less than uniform mixing and/or loss of anti-resorptive particles because residues of anti-resorptive particles will settle and remain on the bottom of the container used to mix the liquid monomer and anti-resorptive particles prior to polymerization.

(d) Simply adding anti-resorptive particles to the particulate polymer component will not result in the "even distribution of the anti-resorptive particles throughout the polymerized bone-cement matrix after polymerization reaction, and/or prevent the anti-resorptive agent from leaching out at different rates and/or in different peripheral areas that will result in non-uniform drug distribution to adjacent tissue." *See*, for example, page 40, lines 25-29, Example 3, page 40 and Figure 4 of the specification.

Applicants' claimed invention recites "the anti-resorptive agent's particle-size distribution is about the same or less than the polymeric bone-cement component's particle-size distribution", which is ***neither taught nor disclosed by Anuta and Lehtinen {emphasis}***. *See*, for example, claims 38 and 77.

(d) **Anuta and Lehtinen do not** teach or disclose the effects of anti-resorptive particles on the effects of the biomechanical properties of the polymerized bone-cement.

(e) **Anuta and Lehtinen do not** disclose or teach a bone-cement for the localized delivery of drugs, such as drugs that inhibit the resorption of adjacent bone, for an extended period of time without affecting the biomechanical properties of the bone-cement. See page 17, lines 27-34.

To reiterate, Applicants respectfully maintain that **Anuta and Lehtinen do not** teach or suggest mixing anti-resorptive agents in the form of particles with the polymer bead component of the bone-cement, nor teach using particles of anti-resorptive agents which have the same or smaller particle-size distribution than the beads in the polymeric bone-cement component of the bone cement to obtain uniform mixture of bone-cement and anti-resorptive particles after polymerization; nor teach using bone-cement as a vehicle for localized, controlled delivery of drugs.

Applicants have unexpectedly discovered that if the particle-size distribution of the anti-resorptive agent is about the same as the bone cement, a uniform mixture will result which prevents clumping thereby promoting the even distribution of the anti-resorptive agent in the composition. *See* for example page 17, lines 20-23. If the anti-resorptive agent is not evenly distributed, the agent may leach out of the polymerized bone-cement at different rates and/or in different peripheral areas resulting in non-uniform drug distribution to adjacent tissue -- a problem that has been encountered in using non-uniform mixtures of bone-cement and anti-resorptive particles.

Applicants respectfully maintain that **Anuta and Lehtinen**, alone or in combination, **do not** teach one of ordinary skill

in the art how to make Applicants' claimed invention, which is a bone-cement composition capable of, for example, bonding prosthetic implants to the living bone of a mammal or human for an extended period of time (*see* page 17, lines 28-32 of the Specification) by locally delivering anti-resorptive agents to the adjacent bone to minimize osteolytic bone resorption. *See* page 16, lines 9-11 of the Specification.

Applicants have also found that local delivery of bisphosphonate pamidronate using a bone-cement of Applicants' claimed invention achieves bone tissue drug levels at least as high as achieved by weekly systemic/oral administration for the period of one year. Equivalent pamidronate levels were achieved by local delivery with only one $15,000^{th}$ of the oral administered dose. See paragraph under the heading "Discussion" of DiResta, et al. Distribution of Pamidronate Bound to Bone Following Local Delivery from Pamidronate-PMMA Bone Cement. Presented at the 51^{st} Annual Meeting of the Orthopaedic Research Society, Washington, D.C. (Feb 2005). A copy of the presentation is attached herein as **Exhibit B**.

In addition, Applicants respectfully maintain that by combining the teaching of Anuta and Lehtinen, one of ordinary skill in the art would not be able to make a bone-cement composition, for bonding prosthetic bones, joints or bone grafts to skeletal tissues, reducing bone voids, etc., which has biomechanical properties that satisfy the minimum standards set by the American Society of Testing and Materials (ASTM). *See* page 38, example 1, and Figures 1 and 2 of the Specification.

Applicants have also developed a mathematical model to simulate radial distribution of bisphosphonate pamidronate from a bone-cement of Applicants' claimed invention. See paragraph under the heading "Background", lines 11-14 of

DiResta, et al. Mathematical Model and Experimental Validation of Local Delivery of Pamidronate to Bone Adjacent to Pamidronate-PMMA Bone Cement. Presented at the 51st Annual Meeting of the Orthopaedic Research Society, Washington, D.C. (Feb 2005). A copy of the presentation is attached herein as **Exhibit C**.

Furthermore, **Anuta and Lehtinen**, alone or in combination, **do not** teach one skilled in the art: (1) how to address the effect of the anti-resorptive particles impregnated within the polymerized bone-cement on the biomechanical properties of the polymerized bone-cement; (2) how to control the release of the anti-resorptive agents from the polymerized bone-cement without affecting the material strength of the polymerized bone cement while inhibiting debris-induced osteolysis, or bonding a prosthetic implant to bone for substantially the life of a patient (*See* page 8, lines 7-9, and page 38, example 1 of the Specification); and/or (3) how to make a bone-cement composition containing anti-resorptive particles {emphasis} uniformly blended/distributed throughout the bone-cement.

Applicants have discovered that the uniform distribution of anti-resorptive particles within the bone-cement composition after polymerization is the result of mixing anti-resorptive particles with the polymeric bone-cement component before polymerization.

Applicants have further discovered that the particle size distribution of the anti-resorptive particles must be the same or less than the particle size distribution of the polymeric component to uniformly distribute the anti-resorptive particles throughout the bone-cement after polymerization, which was not taught or disclosed by Anuta and/or Lehtinen, and which is an inventive aspect of

Applicants' claimed invention. *See* page 17, lines 20-23 of the Specification. Furthermore, Anuta and Lehtinen do not teach whether to blend the anti-resorptive agents with the monomeric or polymeric bone-cement component or both, and whether to mix the anti-resorptive agents before or after polymerization reaction. Accordingly, Applicants' claimed invention, i.e., claims 38-53, cannot be obvious over Anuta and Lehtinen, as indicated by the Examiner on page 2, paragraph 1 of the June 24, 2004 Office Action, and page 3, paragraph 1 of the January 13, 2005 Office Action.

1.5 Combination of Lehtinen and Anuta would change the principle operation of Applicants' claimed invention

The combination of a solution of bisphosphonate with polymeric bone-cement particles would change the principal operation of the Applicants' claimed invention and render it unsatisfactory and inoperable for its intended purpose. In addition, any aqueous solution will inhibit polymerization. *See* for example page 18, lines 35-36 and page 19, lines 1-12. Furthermore, cementing a prosthesis treated with clodronate to the bone of a subject does not read on Applicants' claimed invention because Applicants' claimed invention can, in addition to inhibiting bone resorption and securing prostheses to the bone of a patient, deliver large quantities of drugs directly to the adjacent bone to inhibit osteoclast mediated osteolysis. *See* for example page 37, lines 1-6.

1.6 Combination of Lehtinen and Anuta do not disclose or teach the effect of anti-resorptive particles on the biomechanical properties of the bone-cement

In addition, the combined teachings of **Anuta and Lehtinen do not** disclose, teach or suggest the mechanical effects of anti-resorptive drug, which would require a detailed understanding of chemistry interactions between polymer and the drug. When an anti-resorptive agent is used with bone cement, there is a

physical entrapment (e.g. impregnation) of the anti-resorptive agent in the bone cement. *See* for example page 34, lines 29-32. The success of a formulation depends upon the chemistry of the bone-cement polymer.

Accordingly, for the reasons stated above, Applicants respectfully request the reconsideration and withdrawal of this ground of rejection.

2. Mao et al. and Gayer et al. do not provide teaching or motivation to one skilled in the art to make Applicants' claimed invention as recited in claims 54-76

The Examiner states that "the rejection made in the paper mail 24 June 2004 under 35 U.S.C. § 103(a) over Mao and Gayer is maintained and hereby repeated for the reasons set forth in the previous office action..." *See* page 3, last paragraph of January 13, 2005 Office Action.

The Examiner further states that "it is noted that the features upon which applicant relies (i.e., the method for arresting the process of aseptic loosening attributed to osteoclasts) are not recited in the rejected claim(s)." *See* page 4, lines 1-3 of January 13, 2005 Office Action.

In response, Applicants respectfully traverse Examiner's above ground of rejection.

Applicants' representative claim 54 recites:

54. A composition comprising:

(a) a bone-cement selected from the group consisting of (1) an organic cement, (2) an inorganic cement, and (3) a composite cement; and

(b) an anti-resorptive amount of an anti-resorptive agent

> wherein the anti-resorptive agent is present in an amount that does not compromise the cement's chemical or mechanical properties but sufficient to prevent loosening of the bone cement from the living bone.

Applicants respectfully contend that one of ordinary skill in the art would consider the wording "prevent loosening of the bone cement from the living bone" recited, for example, in claim 54 to also mean "arresting the process of aseptic loosening attributed to osteoclasts" because aseptic loosening of bone-cement from the bone is primarily caused by osteoclasts. *See* Healey JH, Shannon F, Boland P and DiResta GR. PMMA to Stabilize Bone and Deliver Antineoplastic and Antiresorptive Agents. Clinical Orthopedics and Related Research (415 Suppl):S263-75, 2003, **Exhibit D**.

The resorption of bone at the bone-cement interface is almost exclusively due to osteoclast mediated bone resorption. Routine joint replacements undergo typical aseptic loosening entirely by osteoclastic resorption. No other mechanism has been documented. Mechanical pistoning and particulate debris contribute to the generation of osteoclasts that differentiate from macrophage-monocyte cells.

2.1 Mao et al.

Examiner alleged that Mao et al. "teach polymeric materials that can be used to produce surgical devices such as molded appliances (column 7, lines 4-12). The polymers can be used in a composition containing an active substance and can be used to produce a bone cement for repairing injury to bone (column 21, lines 10-16)." *See* page 5, lines 10-13 of the June 24, 2004 Office Action.

Column 7, lines 4-12 of Mao et al., as cited by the Examiner, state:

> We have discovered a new class of synthetic crosslinked polymeric materials and blends that may be used to produce surgical devices such as molded devices, drug delivery matrices, coatings, lubricants and the like. The invention also contemplates a process for producing the crosslinked polymers and blends, and methods for utilizing the subject compositions in the pharmaceutical and/or cosmetic treatment of animals.

Column 21, lines 10-16 of Mao et al., as cited by the Examiner, state:

> The polymers of the present invention can be used either alone or as a composition containing, in addition, a biologically active substance to form a variety of useful biodegradable materials. For example, the polymer of formula I can be used to produce a biosorbable suture, an orthopedic appliance or bone cement for repairing injuries to the bone or connective tissue…

2.2 Gayer et al.

The Examiner alleged that "Gayer et al. teach moldable polymer matrix systems (column 3, lines 43-14) for bone replacement. The polymer may contain hydroxyapatite (column 10, lines 27-31) and osteoconductive factors such as bisphosphonate (column 11, lines 34-38)… It would have been made obvious to one of ordinary skill in the art at the time it was made to substitute zoledronate, pamidronate, etidronate or alendronate for the bisphosphonate of the prior art." *See* last paragraph of June 24, 2004 Office Action.

Column 3, lines 43-47 of Gayer et al., as cited by the Examiner, state:

> The natural, or synthetic, polymer matrix systems described herein are moldable and release BMPs [bone morphogenetic proteins]; however, used alone these polymers serve only as a scaffold for new bone formation.

Column 10, lines 27-31 of Gayer et al., as cited by the Examiner, state:

> Furthermore, the polymer may comprise a polylactic acid-polyethylene glycol copolymer and small particles of hydroxyapatite, salts such as sodium chloride as well as sugars like sucrose, but the embodiment is not so limited.

Column 11, lines 34-38 of Gayer et al., as cited by the Examiner, state:

> Osteoconductive factors used in the polymer-carrier-BMP coating of an embodiment comprise fibrinogen, α-thrombin, anti-inflammatory agents, osteoclast inhibitors such as bisphosphonate…

2.3 Mao et al. and Gayer et al. alone or in combination do not teach a polymerized bone-cement comprising an anti-resorptive agent

Mao et al. and Gayer et al., alone or in combination, do not teach Applicants' claimed invention, which is a composition comprising: (a) a **bone-cement** for **bonding prosthetic** implants to the bone of a patient for substantially the life of the patient and (b) **an anti-resorptive agent** to **prevent loosening** of the bone cement from the living bone. *See*, for example, claim 54.

The bone-cement matrix of the present invention is non-degradable and comprises anti-resorptive agents for inhibiting bone resorption and for drug delivery. The anti-resorptive agents are physically entrapped in the bone-cement matrix, but do not compromise the bone-cement's chemical or mechanical properties. *See*, for example, claim 54.

Applicants respectfully maintain that Mao et al. and Gayer et al. do not disclose, teach or suggest Applicants' claimed

invention. In addition, the combination of Mao et al. and Gayer et al. in an attempt to derive the Applicants' invention would change the principal operation of the Applicants' claimed invention and render it unsatisfactory and inoperable for its intended purpose.

Mao et al., as cited by the Examiner, stated that "[t]he polymers of the present invention can be used either alone or as a composition containing, in addition, a biologically active substance to form a variety of useful **biodegradable** materials. For example, the polymer... can be used to produce... bone cement for repairing injuries to the bone or connective tissue..." *See* column 21, lines 10-16 of Mao et al. In addition, discloses biodegradable polymer compositions that degrade in vivo. *See* abstract of Mao et al.

Gayer et al., as cited by the Examiner, disclose natural, or synthetic, polymer matrix systems which are moldable and release BMPs (bone morphogenetic proteins). *See* column 3, lines 43-47 of Gayer et al.

Applicants respectfully maintain that Gayer et al. teach or disclose:

(1) a prosthetic implant device comprising fibrillar wires or prongs peeled or gouged from the implant core. *See* column 7, lines 11-13 of Gayer et al.

(2) New bone growth is induced to integrate with the structure formed by the system of fibrillar wires. *See* column 8, lines 54-56 of Gayer et al.

(3) To promoted integrated bone growth, **several coating layers** are formed on the fibrillar-wool-wires or prongs and

the prosthetic implant device. *See* column 8, lines 65-67 of Gayer et al.

(4) The third layer is a moldable-polymer-carrier material that localizes osteoconductive factors. *See* column 9, lines 3-4 of Gayer et al.

(5) The purpose of the moldable polymer coating containing osteoconductive proteins is to encourage bone growth into the wool-prosthesis by sequestering the bone-formation-stimulatory-proteins. See column 9, lines 13-15 of Gayer et al.

In the June 24, 2004 Office Action (*See* page 5, last paragraph), the Examiner cited column 11, lines 34-38 of Gayer et al., which states that the "[o]steoconductive factors used in the **polymer-carrier-BMP coating** of an embodiment comprise… osteoclast inhibitors such as bisphosphonate…"

(6) The polymer-carrier-BMP (bone morphogenetic proteins) coating "provides for accelerated bone formation by serving as a reservoir for osteoconductive factors..." *See* column 10, lines 10-11 of Gayer et al.

(7) To work properly, the carrier should **BIODEGRADE** in a timely fashion. *See* column 10, lines 15-17 of Gayer et al.

The combination of Mao et al. and Gayer et al. would result in prosthesis with fibrillar wires coated with biodegradable polymer composition, which if used as a bone-cement for bonding prosthesis to the bone of a patient would ***result in joint failure*** as: (1) the polymer of Mao et al. will degrade over time; (2) the polymer-carrier-BMP (bone morphogenetic proteins) coating of Gayer et al. will also degrade; and (3)

the polymer of Gayer et al. is only used for coating fibrillar wires on a prosthesis to encourage bone growth.

Based on the reasons stated above, Applicants respectfully contend that the disclosure of Mao et al. and Gayer et al. teach one of ordinary skill in the art away from applicants' claimed invention.

Applicants' claimed invention seeks to arrest the process of aseptic loosening attributed to osteoclasts and associated with cemented prosthesis. The anti-resorption agent within the bone cement is a **solid** that is **slowly leached** from the cement directly to the adjacent bone and is intended to stop the process of bone resorption. Bone ingrowth into the cement, is not intended, required or produced. *{emphasis}* The anti-resorption agent cement provides positional alignment and structural stability in addition to its role as a drug delivery system. Please see the table below for a comparison of Applicants' representative claim 54 and Mao et al. and Gayer et al.

Claim 54	**Mao et al.**	**Gayer et al.**
54. A composition comprising:		
(a) a bone-cement selected from the group consisting of (1) an organic cement, (2) an inorganic cement, and (3) a composite cement; and	Synthetic cross-linked polymeric materials and blends that may be used to produce surgical devices such as molded devices, drug delivery matrices, coatings, lubricants and the like. [*See* column 7, lines 4-12 of Mao et al.]	**Teach away - a polymer-carrier-BMP coating** The natural, or synthetic, polymer matrix systems described herein are moldable and release BMPs [bone morphogenetic proteins] [*See* column 3, lines 43-47 of Gayer et al.]
(b) an anti-resorptive amount of an anti-resorptive agent	**Not present**	Osteoconductive factors used in the polymer-carrier-BMP coating of an embodiment comprise osteoclast inhibitors such as bisphosphonate

		[*See* column 11, lines 34-38 of Gayer et al.]
wherein the anti-resorptive agent is present in an amount that does **not compromise the cement's chemical or mechanical properties** but sufficient to **prevent loosening of the bone cement from the living bone.**	**Teach away - biodegradable matrix or polymer** The polymers of the present invention can be used either alone or as a composition containing, in addition, a biologically active substance to form a variety of useful **biodegradable** materials. [*See* column 21, lines 10-16 of Mao et al.]	**Teach away - biodegradable matrix or polymer** The polymer-carrier-BMP (bone morphogenetic proteins) coating "provides for accelerated bone formation by serving as a reservoir for osteoconductive factors..." [*See* column 10, lines 10-11 of Gayer et al.] To work properly, the carrier should **BIODEGRADE** in a timely fashion. [*See* column 10, lines 15-17 of Gayer et al.]

Accordingly, for the reasons stated above, Applicants respectfully request the reconsideration and withdrawal of this ground of rejection.

II. Claim Rejections - 35 USC § 112

The Examiner rejected claims 116 and 118 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *See* page 4, lines 9-11 of January 13, 2005 Office Action.

In response, Applicants have amended claim 116 to depend on claim 38 and canceled claim 118 without prejudice, thereby rendering this ground of rejection moot. Accordingly, Applicants respectfully request the reconsideration and withdrawal of this ground of rejection.

III. Election/Restriction

The Examiner stated that "new submitted claims 118-121 are directed to an invention that is independent or distinct from the invention originally claimed." *See* page 5, first paragraph of January 13, 2005 Office Action.

In response but without conceding the correctness of the Examiner's position and to expedite the prosecution of this Application, Applicants have canceled Claims 118-121 without prejudice. The pending claims do not contain the above mentioned issues, thereby rendering this ground of rejection moot.

IV. New claim rejection - 35 USC § 102

The Examiner rejected claims 54, 61, 70, 77, 78, 80, 86, 93, 98, 100 and 109 under 35 USC § 102(a) as being anticipated by Sabokbar et al. (Ann. Rheum. Dis. October 1998).

The Examiner states:

> Sabokbar et al. teach a polymethylmethacrylate (PMMA) bone cement, mixed with bisphosphonate, etidronate, to inhibit bone resorption (see abstract). Specifically, PMMA was mixed with crushed etidronate and then polymerized accordingly to manufacturer's instructions (see Methods). The extent of resorption was significantly less in the PMMA with etidronate than in PMMA alone suggesting the incorporation of a bisphosphonate into bone cement to inhibit macrophage-osteoclast differentiation may effectively be used to control periprosthetic osteolysis (see discussion). Sabokbar et al teach that bisphosphonates, included in bone cement may be used to prevent or control the bone resorption seen in aseptic loosening (see discussion). *See* page 6, paragraph 1 of the January 13, 2005 Office Action.

In response, Applicants respectfully traverse the Examiner's above ground of rejection for the following reasons:

First, Applicants respectfully maintain that the Examiner's assertion that "PMMA was mixed with crushed etidronate and then polymerized..." is incorrect. Rather, crushed etidronate was mixed to the liquid monomer catalyst and not the PMMA. See paragraph under the heading "Methods" of Sabokbar et al., stating that "EHDP were... then evenly mixed with PMMA monomer..." See also section under the heading "Methods" of abstract of Sabokbar et al., stating that "EHDP were mixed with PMMA monomer before polymerization."

Second, the approach of adding drug particles to the monomer is problematic because the drug particles are not soluble in the monomer and will settle to the bottom of the monomer fluid vial due to gravity. It will be difficult to transfer the drug particles from the monomer fluid vial into the cement. Some drug particles will remain behind and additional monomer fluid cannot be used to flush the remaining material. Also, the use of aqueous fluids will inhibit polymerization. *See* page 19, lines 1-2 of the specification. An additive would be required to ensure that the drug particles remain uniformly suspended within the monomer fluid. As a result, the bone-cement as disclosed by Sabokbar et al. would be less effective and more costly to obtain or make due to drug particle residues remaining on the monomer vial and less then uniform mixing of the drug particles.

Third, Sabokbar does not teach or disclose one of ordinary skill in the art how to obtain a bone-cement wherein the anti-resorptive particles are uniformly distributed within the polymerized bone-cement matrix.

Forth, Applicants' calculations based on Sabokbar et al. indicated that the concentration level of the bone-cement containing etidronate corresponds to 0.094 to 0.374 grams etidronate per 40 grams PMMA. *See* **Exhibit E** for the etidronate level calculation.

Applicants have determined that for drugs to elute out of the polymerized bone-cement matrix at levels that are therapeutically effective, the concentration level of, for example, pamidronate should be 2 grams pamidronate per 40 grams PMMA. *See* page 38, lines 21-24 of the specification.

Therefore, Sabokbar et al. do not teach or disclose a bone-cement comprising an anti-resorptive agent which is "present in an amount that does not compromise the cement's chemical or mechanical properties but sufficient to prevent loosening of the bone cement from the living bone" (*See* claim 54), or which is "evenly distributed throughout the polymerized bone-cement matrix, sufficient to prevent the loosening of the polymerized bone-cement matrix from a living bone to which is it attached for an extended period of time." (*See* claim 77)

Fifth, Sabokbar et al. do not teach to importance of particle sizes of the anti-resorptive agents in producing a polymerized bone-cement with anti-resorptive agents uniformly distributed within the matrix. It is unclear from reading Sabokbar et al. whether the majority (>80%) of the crushed etidronate added to the PMMA cement prior to polymerization of the PMMA cement have particle sizes of between 1-10 microns, or whether the particles sizes are referring to the polymerized-bone-cement-etidronate mixture after crushing and milling for further studies.

If the particles of PMMA/etidronate were being crushed to 1-10 microns for further studies, then the polymerized PMMA-

etidronate particles sizes would not be relevant to the particle size of etidronate added to the PMMA cement. Furthermore if the particle of size of the majority of the etidronate added to the PMMA cement is between 1-10 microns, then 100% of the etidronate within the polymerized matrix will elute out almost instantaneous into the solution being used in the experiment.

All particles within the elution shell regardless of size will leach out. The remainder of the drug within the cement remains permanently trapped because the polymerized matrix is a closed pore structure and water does not diffuse into the matrix past the elution shell. Therefore, the larger the cement volume the greater the amount of drug remains trapped because drug delivery is a function of surface area. *See* **Exhibit F** for drug elution comparison and calculation.

Irrespective of the interpretation by the Examiner regarding the "particle size" in Sabokbar et al., Applicants respectfully maintain that neither interpretation teaches one of ordinary skill in the art the use of particle size of anti-resorptive agents to make a bone-cement comprising uniformly distributed anti-resorptive agents.

Even though vast majority of the anti-resorptive agents remain trapped in the bone-cement matrix of Applicants' claimed invention, the bone-cement of Applicants' claimed invention is capable of eluting out drugs at levels that are therapeutically effective. See page 4, last paragraph of **Exhibit F**. In addition, the local delivery of anti-resorptive agents to the bone region surrounding an implant reduces the incidence of loosening, and prolongs implant longevity. The composition of Applicants' claimed invention also does not compromise the strength of the bone-cement.

Sixth, Applicants respectfully maintain that the Examiner's assertion below regarding the teaching of Sabokbar et al. is incorrect:

> When crushed, the PMMA/etidronate has a particle size of between 1 and 10 microns. Sabokbar et al. teach that the addition of bisphosphonates with PMMA bone cement can inhibit PMMA induced osteoclast generation and bone resorption and inhibit wear debris induced osteolysis and provide a therapeutic approach to prevent aseptic loosening. *See* page 7, lines 12-18 of January 13, 2005 Office Action.

Sabokbar et al. intentionally crushed the polymerized PMMA bone-cement into tiny particles to create PMMA-etidronate debris and test whether injected debris would inhibit macrophage differentiation. *See* paragraph under the heading "Discussion", first paragraph, last sentence of Sabokbar et al. The cells that ingested the etidronate-PMMA debris were affected and not the bone. **Sabokbar et al. never treated the bone directly to observe if the osteoclasts were inhibited**.

In contrast, the bone-cement of Applicants' claimed invention inhibits the resorption of osteoclasts activity by protecting the bone with anti-resorptive agents, such as bisphosphonates, that leaches to the bone. The bone in direct contact with the polymerized PMMA is treated. *See* **Exhibit B.**

Macrophage-osteoclast differentiation continues through the life of the patient because of the continuous production of debris by normal movement of the joint components against each other. Protecting the bone is the objective. While some PMMA debris forms this material is likely to have had its entire drug content leached out because the PMMA debris and breakdown is a surface phenomenon, exactly the area from which all the drug would elute.

The concept of cement induced osteolysis, which is the focus of the study by Sabokbar et al., is an antiquated one, based on early, incomplete understanding of the basis of prosthetic osteolysis.

Cement particulate debris is the smallest contributor to the problem in quantitative and qualitative terms. It is well established the predominant contributor to particle induced osteolysis is sub micron particles of polyethylene and to a lesser extent, metal (titanium) debris. *See* page 114, column 2, lines 5-10 of Chiba J. Schwendeman LJ. Booth RE Jr. Crossett LS. Rubash HE.A biochemical, histologic, and immunohistologic analysis of membranes obtained from failed cemented and cementless total knee arthroplasty. Clinical Orthopaedics & Related Research. (299):114-24, 1994 Feb., **Exhibit G**. *See also* paragraph under the heading "Discussion" of SHANBHAG A.S, HASSELMAN C.T, KOVACH C.J., and H.E. RUBASH POSSIBLE UPREGULATION OF MACROPHAGE RESPONSIVENESS TO WEAR DEBRIS. 45th Annual Meeting, Orthopaedic Research Society, February 1-4, 1999, Anaheim, California, attached as **Exhibit H**, stating that "control canine macrophages clearly demonstrate the intense stimulatory nature of wear debris, particularly PE [polyethylene]…" These papers demonstrate that it is the debris type, i.e., polyethylene, that is most influential in inducing osteolysis.

Sabokbar et al. specifically use particles of 1-10 microns of PMMA, those that induce a different qualitative and quantitative reaction than the submicron polyethylene.

The following literature presents data indicating that the majority of debris isolated from periprosthetic membrane is sub-micron. *See* abstract of Campbell P, Ma S, Yeom B, McKellop H, Schmalzried TP, Amstutz HC Isolation of predominantly submicron-sized UHMWPE wear particles from

particles were clearly observed and were either rounded or elongated. The majority were submicron in size."

The following literature identifies the importance of sub-micron particles on macrophage activity. *See* abstract of T.R. Green, J. Fisher, M. Stone, B.M. Wroblewski. E. Ingham. Polyethylene particles of a 'critical size' are necessary for the induction of cytokines by macrophages in vitro. Biomaterials 19 (1998) 2297-2302, attached as **Exhibit J**, stating that "polyethylene particles are critical factors in macrophage activation." The most sensitive range was 0.49-4.3 microns.

These differences are significant and show that the teaching of Sabokbar et al. relates to a tangential and largely irrelevant phenomenon.

Swearing behind Sabokbar et al. Reference

Lastly, Sabokbar et al. do not anticipate Applicants' claimed invention because Sabokbar et al. was published in October 1998, which is after Applicants' invention disclosure of **March 1998** and less than one (1) year prior to the February 9, 1999 effective filing date of this Application. A copy of Applicants' redacted Invention Disclosure Form is attached herein as **Exhibit K**. Applicants will submit an affidavit or declaration under 37 CFR § 1.131 if requested by the Examiner, or, alternatively, if the Sabokbar et al. reference is not withdrawn by the Examiner in light of the arguments presented above.

2. Summary

In summary, Applicants have discovered that the uniform distribution of anti-resorptive agents within the bone-cement can be achieved, for example, by mixing particles of anti-resorptive agent with the dry/particulate polymer component of the bone-cement prior to polymerization. To obtain uniform mixture of bone-cement and anti-resorptive particles/agents, Applicants have also discovered that the particle size distribution of the anti-resorptive agent to be mixed with the dry polymer component should be the same or less than the particle size distribution of the dry polymer component of a particular bone-cement.

Applicants have further discovered that the uniform distribution of particles within the bone-cement enables the bone-cement to serve as an effective vehicle for *localized, controlled, extended* delivery of anti-resorptive agent and/or other drugs to the adjacent bone to arrest or prevent bone resorption.

Accordingly, for the reasons stated above, Applicants respectfully request the reconsideration and withdrawal of this ground of rejection.

V. Claim Rejections - 35 USC § 103

1. Claims 38-53 are not obvious over Anuta and Sabokbar et al.

The Examiner rejected claims 38-53 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Anuta and Sabokbar et al.

The Examiner states:

> It would have been made obvious to one of ordinary skill in the art at the time it was made to employ the recited particle sizes motivated by the recitation of Anuta that Zimmer's standard bone cement employs a mixture of 65 to 70% polymer beads with a maximum size of 25 microns and 30 to 35% of the beads have been milled (column 5, lines 43-47) and a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns (column 6, 59-63) and add the bisphosphonate powder of Sabokbar, such a modification would have been motivated by the reasoned expectation of producing a bone cement composition which is effective in comprehensively preventing osteoclast formation and loosening of prostheses. *See* page 7, paragraph 3 of the January 13, 2005 Office Action.

In response, Applicants respectfully traverse the Examiner's above ground of rejection. Applicants' bone-cement comprises a uniform mixture of bone-cement and anti-resorptive agent. The particles of anti-resorptive agent are mixed with the polymer component of a bone-cement prior to polymerization. The particles of the anti-resorptive agent are processed to obtain a particle size distribution which is similar or less than the particle size distribution of the polymer component before mixing. Thus, Sabokbar et al. and Anuta, alone or in combination, do not teach or disclose the above-mentioned improvements discovered by the Applicants.

The table below is a comparison of Sabokbar et al. and Anuta and bone-cement of Applicants' claimed invention.

Sabokbar et al. *See* page 7, lines 13-19 of January 13, 2005	**Anuta** *See* page 7, lines 6-11 of January 13, 2005	**Bone-cement of Applicants' claimed invention**

Office Action	Office Action	
"PMMA bone cement with the bisphosphonate etidronate incorporated into the bone cement." "The composition is mixed and polymerized." **Etidronate is mixed with the liquid monomer component**	Zimmers standard bone cement. "It does not teach the addition of a bisphosphonate."	Bone-cement comprising a polymer and a monomer component. [*See*, for example, claim 77] Anti-resorptive agents are mixed with the polymer bone-cement component prior to polymerization. [*See*, for example, claim 77]
"When crushed, the PMMA/etidronate has a particle size of between 1 to 10 microns." **The particle size of the crushed PMMA/etidronate is irrelevant to Applicants' claimed invention** **The particle size of the crushed PMMA/etidronate was used to simulate PMMA wear debris**	"The polymethylmethacrylate (PMMA) powder in Zimmers standard bone cement is comprised of a mixture of 65 to 70% polymer beads with a maximum average size of 25 microns and 30-35% of the beads have been milled (column 5, lines 43-47) and a bead fraction where the bead powder is sifted to a size range of 13-17 microns (column 6, lines 59-63)." **Anuta only disclose or teach the particle size distribution of the PMMA/polymer component of Zimmer's standard bone cement.** **Anuta does not teach adding bisphosphonate or any drug to the bone cement.**	The anti-resorptive agent's particle-size distribution is about the same or less than the polymeric bone-cement component's particle-size distribution [*See*, for example, claim 38]

"Sabokbar et al. teach that the addition of bisphosphonate with PMMA bone cement can inhibit PMMA induced osteoclast generation and bone resorption and inhibit wear debris induced osteolysis and provide a therapeutic approach to prevent aseptic loosening." **Sabokbar et al. do not teach using bone-cement comprising anti-resorptive agents to treat adjacent bone, rather it crushed the polymerized PMMA cement to simulate PMMA wear debris and test whether debris from PMMA cement mixed with etidronate would be able to inhibit osteoclast differentiation by macrophages.** **The PMMA cement of Sabokbar et al. would not be useful for treating adjacent bone because the amount of etidronate used is too small and the etidronate trapped within the polymerized PMMA cement would not elute out at levels that are therapeutically effective.** **Sabokbar et al. only address a specific problem related to prosthesis implant, which is to prevent osteolysis associated with PMMA debris produced during normal movement of the implant.** **Applicants' bone-cement treats the adjacent bone, not just the**		A local drug delivery system [See, for example, claims 38 and 77] The anti-resorptive agent is uniformly distributed within the polymerized bone-cement [See, for example, claim 77]

debris.		

Accordingly, for the reasons stated above, Applicants respectfully request the reconsideration and withdrawal of this ground of rejection.

2. Claims 54-117 are not obvious over Anuta and Sabokbar et al., and further in view Merck and Co., Inc.

The Examiner rejected claims 54-117 under 35 U.S.C. 103(a) as being unpatentable over Sabokbar et al.; and over Sabokbar et al. and Anuta as applied to claims 38-53 above, and further in view of Merck and Co., Inc. WO 96/39107.

The Examiner states:

> It would have been made obvious to one of ordinary skill in the art at the time it was made to employ the recited particle sizes motivated by the recitation of Anuta that Zimmer's standard bone cement employs a mixture of 65 to 70% polymer beads with a maximum size of 25 microns and 30 to 35% of the beads have been milled (column 5, lines 43-47) and a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns (column 6, 59-63) and add the bisphosphonate powder [etidronate] of Sabokbar, such a modification would have been motivated by the reasoned expectation of producing a bone cement composition which is effective in comprehensively preventing osteoclast formation and loosening of prostheses. See page 9, paragraph 3 of the January 13, 2005 Office Action.

The Examiner concedes that Anuta and Sabokbar et al do not "teach the addition of other bisphosphonates."

The Examiner further states:

> Merck and Co. teach the addition of further bisphosphonates to the cement. The bisphosphonate applicable in the cement includes the free acid and pharmaceutically acceptable salts and barium salts of alendronate, clodronate, tiludronate, YM 175, ibandronate, risedronate, piridronate, pamidronate or combination thereof (see page 5)... The PMMA beads have a substantially uniform particle size of about 5 to 20 microns average diameter (page 7 last paragraph)... The amount of bisphosphonate is generally from 0.005 to 10 percent of the total cement composition. It would have been made obvious to one of ordinary skill in the art at the time it was made to add additional bisphosphonates as cited in Merck and Co. Such modification would have been motivated by the reasoned expectation of producing a bone cement/bisphosphonate composition which is effective in comprehensively preventing formation of osteoclasts and loosening of prosthetic implants. *See* page 10, paragraph 1 of the January 13, 2005 Office Action.

In response, Applicants respectfully traverse the Examiner's above ground of rejection.

The bone-cement of Applicants' invention comprises anti-resorptive agent uniformly distributed within the polymerized bone-cement matrix. The particles of anti-resorptive agent are mixed with the polymer component of a bone-cement prior to polymerization. The particles of the anti-resorptive agent are process to obtain a particle size distribution which is similar or less than the particle size distribution of polymer component before mixing. Neither Anuta nor Sabokbar et al. nor Merck & Co., Inc., et al., alone or in combination, disclose or teach the particle size distribution of the anti-resorptive agent used in the bone-cement of Applicants' claimed invention.

Accordingly, for the reasons stated above, Applicants respectfully request the reconsideration and withdrawal of this ground of rejection.

Conclusion

Applicants believe that the above arguments address all issues raised in the January 13, 2005 Office Action and respectfully request the reconsideration and withdrawal of all ground of rejections pending in this application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891.

I hereby certify that this paper is being deposited this date with the U.S. Postal Service with sufficient postage for first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Albert Wai-Kit Chan 4/11/05
Albert Wai-Kit Chan Date
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